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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,380	SAITO ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,18 and 21* is/are rejected.

7)☒ Claim(s) *11-17,22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 8 December 2004 in response to the Non-Final Office Action mailed 9 June 2004. Claims 1-20 were pending and claims 19 and 20 were withdrawn from consideration in the previous Office Action. Claims 1-7 and 9-18 were amended, claims 19 and 20 were canceled and claims 21 and 22 were added in the 8 December Paper. Claims 1-18, 21 and 22 are presently pending.

Response to Amendments and Arguments

Claim Objections

Objection to claim 9 as being in improper form **is withdrawn** in view of the amendment of the claim such that it is no longer improperly multiply dependent.

Claims 11-17 **stand objected to** and newly added claim 22 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Specifically, claims 11-16 are multiply dependent and depend from claim 10, which in turn depends from multiply dependent claim 3. Claims 17 and 22 are improperly dependent insofar as they depend from improper multiple dependent claims 15 or 16, respectively. See MPEP § 608.01(n). Accordingly, claims 11-17 and 22 have not been further treated on the merits.

Objection to claims 5-7 and 10 as containing informalities **is withdrawn** in view of the amendments to the claims.

Claim Rejections - 35 USC § 101

Rejection of claims 1-3 and 18 under 35 U.S.C. 101 as directed to non-statutory subject matter **is withdrawn** in view of the amendment of claims 1-3 such that they are directed to "an isolated" DNA, which clearly evidences the hand of man, and the amendment of claim 18 such that it is directed to a "transgenic non-human animal".

Claims 4-7 **stand rejected** under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

As stated in the previous Office Action, the claims do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products.

In response to the *prima facie* case of record, Applicant argues that a DNA comprising a FRT sequence comprising any one of SEQ ID NO: 2-5 are not found in nature and urges that because of this the DNA of claim 1 is an artificial DNA made by the hand of man.

This argument has been fully considered but is not deemed persuasive. First it is noted that the claims that stand rejected are not limited to comprising the isolated DNA of claim 1. Instead, the claims need only comprise a wild type FRT sequence and "at least one mutant FRT sequence defined in claim 1". As discussed in the previous Office Action, mutations occur naturally and, therefore, the mutant FRT sequences of the claims could arise spontaneously, absent the hand of man. Applicant's assertion that a FRT sequence comprising one of SEQ ID

NO: 2-5 is not found in nature is unfounded because, obviously, not all naturally occurring FRT recombination sites have been sequenced and there is no reason to believe that a FRT site comprising the sequence set forth as SEQ ID NO: 2-5 could not arise spontaneously.

Claim Rejections - 35 USC § 112, first paragraph

Claims 8, 10 and 18 **stand rejected**, newly added claim 21 **is rejected**, and claim 9 is **newly rejected** (necessitated by amendment of claim 9 such that it is no longer improperly multiply dependent) under 35 U.S.C. 112, first paragraph, as lacking a fully enabling disclosure for reasons of record.

The claims were rejected on the grounds that the specification, while being enabling for a method for replacing a gene *in vitro* and a cell transformed with the DNA comprising a mutant FRT sequence of the invention *in vitro*, does not reasonably provide enablement for the method practiced *in vivo*, a cell transformed with the DNA of the invention *in vivo* or a transgenic animal comprising the DNA of the invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to the *prima facie* case of record, Applicant first asserts that the Examiner errs by focusing the rejection on the predictability of gene therapy because the claims are not limited to gene therapy. This argument has been fully considered but is not deemed persuasive. Enablement for gene therapy was considered in making the rejection because a substantial portion of the teachings in the specification with regard to how to use the claimed invention *in*

vivo concerns gene therapy. However, the unpredictability of gene therapy was, by no means, the only basis for finding that the claims were not enabled.

In the first paragraph on page 6, the Office Action states:

> Upon reviewing the art, the Examiner is unable to find a single working example of *in vivo* gene replacement using the FLP recombinase system. Although two reports of *in vivo* gene deletions using FRT repeats flanking a gene were available in the art at the time of filing (*i.e.*, Dymecki (1996) *Proc. Natl. Acad. Sci. USA* 93:6191-619 and Vooijs *et al.* (1998) *Oncogene* 17:1-12), there are no examples of a method wherein a gene was inserted into a genome *in vivo* using FLP recombinase. The art is silent with regard to failed attempts at practicing a method according to the instant claims; however, one of ordinary skill in the art would reasonably expect that the efficiency of a method requiring only a single intramolecular recombination (*i.e.*, deletion of a gene as demonstrated in the art) would be much higher than the efficiency of a method that requires two recombination events between two separate molecules. Thus, the limited success in applying FRT recombinase to obtaining *in vivo* gene deletions does not reasonably support enablement for a method that is logically much less efficient.

In the paragraph bridging pages 11-12, the Office Action states:

> Although the relative level of skill in the art is high, practicing the claimed invention *in vivo* would clearly require experimentation beyond what is routine in the art. It cannot be said that developing a technology demonstrated to be effective in a cell free extract such that it can be used *in vivo* is routine if the technology has never been practiced successfully *in vivo*. In the instant case, the art is silent with regard to applying FLP recombinase mediated gene replacement to obtain a useful, or even measurable, phenotypic change in an animal. The instant disclosure provides mutant FRT sequences having essentially the same activity as the FRT sequences that were known in the art at the time of filing and general teachings directed to making transgenic animals and therapeutic gene replacement. Given that the teachings provided are no different than what was already available to the skilled artisan at the time of filing, the art recognized unpredictability of obtaining gene replacement of sufficient degree to provide a useful effect and the absence of any working examples of the *in* vivo application of the claimed invention even 5 years after the effective filing date of the application, practicing the claimed invention commensurate with its full scope would clearly require experimentation beyond what is considered routine in the art.

Thus, contrary to Applicant's assertion, the basis for the finding of lack of enablement is the unpredictability of obtaining a useful degree of gene replacement *in vivo* using a method that requires an intermolecular double reciprocal crossover event. As discussed in making the rejection, such an event would be expected to occur at a very low frequency and there is not a single example of an operative *in vivo* method of replacing a nucleotide sequence by reacting a first DNA comprising in sequential order a wild type FRT sequence, a first nucleotide sequence of interest and a mutant FRT sequence with a second DNA comprising in sequential order a wild type FRT sequence, a second nucleotide sequence of interest and a mutant FRT sequence which is identical to the mutant FRT sequence of the first DNA in the presence of recombinase FLP.

Applicant points to teachings in the specification that allegedly support the claimed method practiced *in vivo*, but these examples are merely prophetic and, while the substitution reaction might occur at some low frequency *in vivo*, the skilled artisan would not expect, given the technology available at the time of filing, to be able to obtain a useful outcome practicing the claimed gene substitution reaction with a cell *in vivo*.

Applicant cites several articles which are alleged to be examples of *in vivo* gene replacement mediated by a site-specific recombinase. However, none of the cited articles is, in fact, an example of *in vivo* gene replacement. Lakso *et al.* teaches cre dependent activation of TAg expression by excision of a floxed (flanked by lox recombination sites as direct repeats) stop cassette (Fig. 1); Orban *et al.* teaches excision of a floxed β-galactosidase gene (Fig. 1); Kuhn *et al.* teaches excision of a floxed polβ gene (Fig. 1); Akagi *et al.* teaches excision of a floxed CAT gene (Fig. 1); and both Wang *et al.* and Wakita *et al.* teach activation of gene expression by excision of a floxed stop cassette. Thus, the teachings in the cited art are

essentially the same as the teachings of Dymecki and Vooijs *et al.*, which were discussed on page 6 of the previous Office Action, and are fundamentally different from the process and products of the instant claims. The processes of claims 9 and 10 are directed to obtaining replacement of a nucleic acid on one DNA with a different nucleic acid on a different DNA, and the products are configured so as to prohibit the intramolecular recombination event that is the basis for the methods practiced in the cited art. Whereas the nucleic acids used in the art comprise direct repeats of the LOX or FRT recombination sites flanking the gene to be excised, and therefore mediate intramolecular recombination (illustrated in the left panel of Figure 1on page 14 of the 8 December Paper), the FRT sites flanking the nucleic acids of the instant claims are incapable of intramolecular recombination (illustrated in the right panel of Figure 1). Thus, the methods cited by applicant do not support what is being claimed in the instant application. As stated in the previous Office Action, there is not a single working example of *in vivo* gene replacement using the FLP or any other site-specific recombinase system either in the art or in the instant application. Given the obviously undeveloped state of the relevant art and the unpredictability of obtaining a useful product by a method that requires an intermolecular double reciprocal cross over *in vivo*, developing the claimed method and product to the point where they can be used as contemplated would require undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. Therefore, the claims stand rejected under 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 112, second paragraph

Rejection of claims 2, 3, 6, 7 and 10 under 35 U.S.C. 112, second paragraph, as being indefinite for reasons set forth in the previous Office Action **is withdrawn** in view of the amendments.

Claim Rejections - 35 USC § 102

Rejection of claims 2, 3, 6, 7 and 10 under 35 U.S.C. 102(b) as being anticipated by either one of Schlake or Seibler *et al.* **is withdrawn** in view of the amendment of the claims such that the mutant FRT sequence is limited to comprising SEQ ID NO: 2.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-10, 18 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a **new matter** rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states,

"[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

Claim 1 has been amended such that it is directed to an isolated DNA encoding a mutant FRT sequence derived from a yeast 2μ DNA comprising SEQ ID NO: 2. As there is no limitation on the extent of derivatization of the yeast 2μ DNA the claim now encompasses any mutant FRT sequence comprising SEQ ID NO: 2, while the mutant FRT sequence was previously limited to comprising sequence set forth in SEQ ID NO: 1 flanking the spacer sequence set forth in SEQ ID NO: 2. Although the application as filed contemplates FRT sequences comprising mutations outside of the spacer region, these sequences were subject to the provisos set forth in, for example, claim 2 (*i.e.*, causing no specific DNA recombination reaction with wild type FRT and causing specific DNA recombination reaction with another mutant FRT sequence having an identical sequence thereto). As the mutant FRT sequence of claim 1, and claims 3-10, 18 and 21 as they depend therefrom, is not subject to these provisos, the claims

embrace subject matter that was not contemplated in the original disclosure and, therefore, comprise new matter.

Claim 18 is further rejected because, as stated in the previous Office Action, "[t]he Examiner can find no support in the specification for a subgenus or species of transgenic animal that excludes humans" (page 4, first full paragraph). In spite of this, Applicant provides no statement of where support for the new limitation can be found in the application as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 6, 7, 10 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in referring to "nucleotide positions 14-21 in the mutant FRT sequence defined in claim 1". As amended, claim 1 defines only 8 nucleotide positions, i.e., those nucleotides set forth in SEQ ID NO: 2. Therefore, there is no antecedent basis for the limitation.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636